

Clozaril[®] (clozapine) Tablets

Briefing Document for Psychopharmacological Drugs Advisory Committee Meeting (November 4, 2002)

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1 PURPOSE OF MEETING

Data from the International Suicide Prevention Trial (InterSePT/ Study ABA 451) supported the Supplemental New Drug Application for Clozaril that was submitted to the Food and Drug Administration (FDA) on February 28, 2002. Following priority review, an “approvable” action was taken on the application on August 30, 2002. The purpose of this Advisory Committee Meeting is to review the results of InterSePT and to determine whether these results justify the proposed indication for Clozaril®.

2 SUICIDAL BEHAVIOR IN SCHIZOPHRENIA

Suicidal behavior in schizophrenia and related psychiatric disorders is a significant public health problem that has not been adequately addressed. Suicidal behavior is characterized by communicated behavior (suicidal thoughts and plans) and observed behavior (suicide attempts that may or may not be successful). Research in this area indicates that suicidal behavior occurs independent of psychosis and positive or negative symptoms (Meltzer and Okayli 1995). In patients with schizophrenia, 40% report suicidal thoughts (McGlashan 1984), between 20 and 40% attempt suicide (Harkavy-Friedman et al, 1999, Heila et al. 1998, Niskanen et al. 1973, Planansky and Johnston 1971) and approximately 4-13% end their lives by suicide (Osby et al. 2000, Heila et al. 1997, Newman 1991, Cohen 1990, Allebeck 1989, Drake, et al. 1985, Nyman and Jonsson 1986, Roy 1986, Bleuler 1978, Tsuang 1978). Of all schizophrenic patients attempting suicide, it is estimated that 1 to 2 % commit suicide within a year after their initial attempts, with an additional 1% doing so each year thereafter (Ettlinger 1975, Kreitman 1977). In addition to prior suicide attempts, a history of multiple psychiatric hospital admissions and a recent discharge from hospital were found to be significant risk factors for suicide (Rossau and Mortensen, 1997). It has been estimated that the total direct and indirect costs of suicidal behavior, including completed suicides, was \$ 45.6 billion in the US in 1994 alone (Palmer et al. 1995). It is clear that treatment that reduces the number of suicide attempts, and attempt-related hospitalizations would reduce the associated social and economic burden.

3 EVIDENCE FOR EFFECT OF CLOZARIL AND ZYPREXA ON SUICIDAL BEHAVIOR

3.1 Clozaril®

Since Clozaril was first marketed in Europe in the mid-1970's, a number of reports have appeared suggesting that Clozaril has an effect on suicidal behavior in patients with schizophrenia (refer to Appendix 2). Other signals of a Clozaril effect on suicidal behavior that led to the development of the InterSePT protocol included results from the following three retrospective studies.

1. Meltzer and Okayli (1995) reported that the percentage of patients with no suicidal behavior of any type increased from 53% during the two years prior to clozapine treatment to 88% during the two-year clozapine treatment period. Specifically, there was an 86% decrease in suicide attempts in 88 treatment-resistant patients with schizophrenia or schizoaffective disorder.
2. Using the Clozapine National Registry (CNR) to classify 57,681 patients as “current,” “recent,” or “past” users of clozapine, Walker, et al. (1997) reported a standardized mortality rate (SMR) from suicide of 39 (deaths per 100,000 person-years) for current clozapine users while recent and past users had an SMR from suicide of 246 and 222, respectively.
3. Reid, et al. (1998) examined annual suicide rates over a 2-year period among an annual average of 30,130 patients with schizophrenia or schizoaffective disorder. Suicide rates in a subgroup of 1,367 patients treated with clozapine were evaluated over a 6-year period. The annual standardized suicide rate for the subgroup of clozapine-treated patients was 12.74 compared to 63.1 per 100,000 for the total study population.

3.2 Zyprexa®

To date, no prospective study has evaluated the effects of the more recently introduced atypical antipsychotic medications on schizophrenic or schizoaffective patients at high risk for suicide. The results of a double-blind study by Tran et al. (1997) comparing olanzapine and risperidone in patients with schizophrenia, schizophreniform or schizoaffective disorder showed the rate of suicide attempts, based on treatment-emergent adverse events, to be statistically significantly lower with olanzapine than risperidone. Also, a post hoc review of clinical data on Zyprexa in patients with schizophrenia suggested a reduction in the annual suicide attempt rate for Zyprexa-treated patients compared to haloperidol-treated patients (Glazer, 1998).

3.3 Considerations for A Prospectively Designed Study in Suicidal Behavior

Taken together, the studies summarized above indicate an association between treatment with Clozaril and Zyprexa and a reduction in suicidal behavior in schizophrenic and schizoaffective patients. However, these studies were all retrospective and did not compare the putative effects of Clozaril on suicidal behavior with effects of the more recently introduced “atypical” antipsychotics. To address these limitations, the InterSePT study was designed as a prospective, randomized, parallel group study to evaluate reduction in suicidal behavior during treatment with Clozaril.

During protocol development, the Neuropharmacological Drug Products Division of the FDA was consulted regarding the study design, in particular regarding the following points:

- 1) **Definition of Endpoints:** It was decided that the efficacy of Clozaril for treating suicidal behavior would be measured using specific endpoints that included suicide attempts, including completed suicides, and hospitalizations to prevent suicide. In addition, an assessment of the patient's change in suicidal behavior from baseline conducted by a blinded clinician would be included (*The Clinical Global Impression of Severity of Suicidal Behavior (CGI-SS) was developed for this purpose*).
- 2) **Choice of Comparators:** Having a placebo arm in the study was considered to be unethical in a study involving an at-risk patient population. Therefore, it was agreed to incorporate an active comparator into the study design (*Zyprexa was selected as the comparator*).
- 3) **Timing of Assessments/Visit Frequency:** The number of evaluations required for white-blood-cell (WBC) monitoring of Clozaril were to be balanced by having an equivalent number of patient contacts for the comparator treatment.
- 4) **Study Blinding:** Because of the necessary WBC monitoring for Clozaril patients, blinding of the study would be impractical. An open-label design would be acceptable, provided that each case exhibiting potential suicidal behavior was to be evaluated by a blinded Suicide Monitoring Board composed of experts in suicidology who were not working with the participating sites.

4 STUDY ABA 451 (InterSePT)

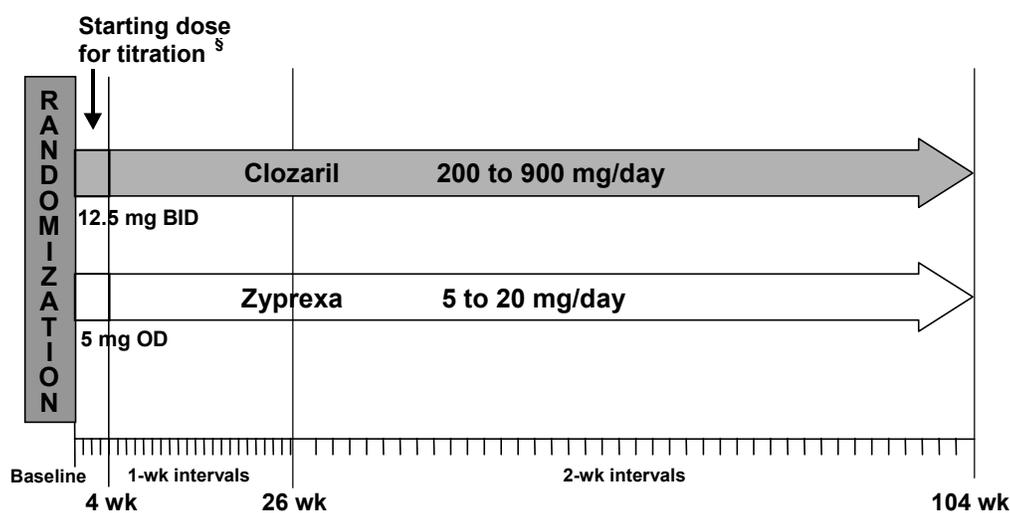
4.1 Study Objective

The primary objective of this study was to demonstrate that treatment with Clozaril compared with Zyprexa decreases the risk of suicide among patients with schizophrenia and schizoaffective disorder. However, it should be pointed out that the statistical analysis for InterSePT is based on suicidal behavior (including suicide attempts, suicides and hospitalizations to prevent suicide) and not suicide as the primary endpoint.

4.2 Study Design

Following randomization to either Clozaril or Zyprexa, patients entered a four-week titration phase, during which patients who were on other antipsychotic medications had their dosage reduced while the dose of study medication was increased. The starting dose of study medication was either Clozaril 12.5 mg b.i.d. or Zyprexa 5.0 mg o.d. (Figure 1).

Figure 1 Study Design Schema



§Transition from previous antipsychotic medication ends at Week 4.

The recommended dosage range was 200 to 900 mg for Clozaril and 5 to 20 mg for Zyprexa. After reaching 5 mg/d of Zyprexa or 200 mg/day of Clozaril, the dosage was adjusted at the discretion of the investigator. Blood monitoring requirements dictated that all Clozaril patients were seen weekly for the first twenty-six weeks and every 2 weeks thereafter until the end of their participation in this 2-year study. To balance the possible confounding effects of this frequent patient contact with study personnel, all Zyprexa patients were seen for vital sign monitoring at the same frequency.

4.2.1 Patient Selection Criteria

In order to qualify for inclusion into the study, patients had to have a diagnosis of schizophrenia or schizoaffective disorder and be at high risk for suicide. To be considered at high risk for suicide, patients had to meet at least one of the following criteria:

- A suicide attempt within the last 3 years
- A hospitalization to prevent suicide in the last 3 years
- Suicidal ideation with depressive symptoms within 1 week of baseline
- Moderate to severe suicidal ideation and self-harm command hallucinations within 1 week of baseline

4.3 Definition of Endpoints

4.3.1 Endpoints for the primary analysis

The primary efficacy objective was to demonstrate decreased risk for suicide among schizophrenic or schizoaffective patients treated with Clozaril compared to that for patients

treated with Zyprexa, as measured by time (in days, after randomization) to the following two types of events:

Type 1 Event:

- Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance), as confirmed by the blinded Suicide Monitoring Board.

Type 2 Event:

- Occurrence of a worsening of severity of suicidal behavior to level 6 or 7 (“much worse” or “very much worse”) on the change score of the Clinical Global Impression of Severity of Suicidality as measured by the Blinded Psychiatrist.
- Because the occurrence of a suicide attempt or hospitalization to prevent suicide implied a worsening of severity of suicidality, every Type 1 event was also considered a Type 2 event.

4.3.2 Secondary endpoints

The key pre-defined secondary efficacy endpoints were as follows:

- 1) Change from baseline on the Positive and Negative Syndrome Scale (PANSS)
Rated in accordance with a rating manual provided to all sites (Kay, et al 1988).
- 2) Change from baseline on the Calgary Depression Scale (CDS)
A 9-item scale. The interviewer rates the patients on each item from 0-3. 0=absent, 1=mild, 2=moderate and 3=severe. (Addington, 1993, Addington, 1994)
- 3) Change from baseline on the Covi Anxiety Scale (Covi)
A 3-item scale. The interviewer rates patients on each item from 0-4. 0= not at all, 1=somewhat, 2=moderately, 3=considerably, 4= very much.
- 4) Change from baseline on the InterSePT Scale for Suicidal Thinking (ISST-PI): A 12-item scale adapted from The Scale for Suicide Ideation (Beck et al., 1979).
- 5) Change from baseline on the Clinical Global Impression of Severity of Suicidality (CGI-SS): derived from the original CGI (Guy 1976), the CGI-SS encompasses a 5-point severity score assessment and a 7-point change score assessment.

4.4 Roles and Responsibilities

The roles and responsibilities of the key personnel involved in the conduct of the study are described below and the flow of information among these individuals is illustrated in Figure 2.

- **Principal Investigator**

The Principal Investigator (PI) was responsible for identifying potential Type 1 events, i.e., suicide attempts, suicides and hospitalizations due to imminent risk of suicide. The PI

forwarded all relevant information concerning potential Type 1 events to the Medical Monitor at the Contract Research Organization (CRO) designated by the Sponsor. The PI was also responsible for overall study conduct at his/her respective site and for completing the following assessments:

- 1) InterSePT Scale for Suicidal Thinking (ISST-PI)
- 2) Clinical Global Impression of Severity of Suicidality (CGI-SS-PI)

- **Blinded Psychiatrist**

A psychiatrist at the investigative site who was blind to the patients' treatment assignments was responsible for completing the following efficacy assessments:

- 1) Clinical Global Impression of Severity of Suicidality (CGI-SS-BP): The blinded psychiatrist performed the CGI-SS evaluation at intervals of 8 to 12 weeks. The CGI-SS-BP was used as a component of the primary endpoint (Type 2 event).
- 2) InterSePT Scale for Suicidal Thinking (ISST-BP): Identical to the ISST-PI and performed at all scheduled and unscheduled visits. This assessment was used as a secondary outcome measure.

The blinded psychiatrist also reviewed the same material that was forwarded to the Suicide Monitoring Board and made an independent determination of whether criteria for a suicide attempt or a hospitalization to prevent suicide were met.

- **Blinded Rater**

A psychiatrist or trained rater at each investigative site who was blind to the patients' treatment assignments was responsible for completing the following efficacy assessments:

- 1) PANSS Positive and Negative Syndrome Scale.
- 2) Calgary Depression Scale
- 3) Covi Anxiety Scale

- **Medical Monitor and Clinical Research Organization (CRO)**

A Clinical Research Organization (Ingenix Pharmaceutical Services, Inc.) was employed to manage the logistical aspects of the InterSePT study. Information related to a suicide attempt, suicide, or hospitalization for imminent risk of suicide was reviewed and blinded by the Medical Monitor of the CRO and sent to the Suicide Monitoring Board (SMB) and the Blinded Psychiatrist (BP) for review.

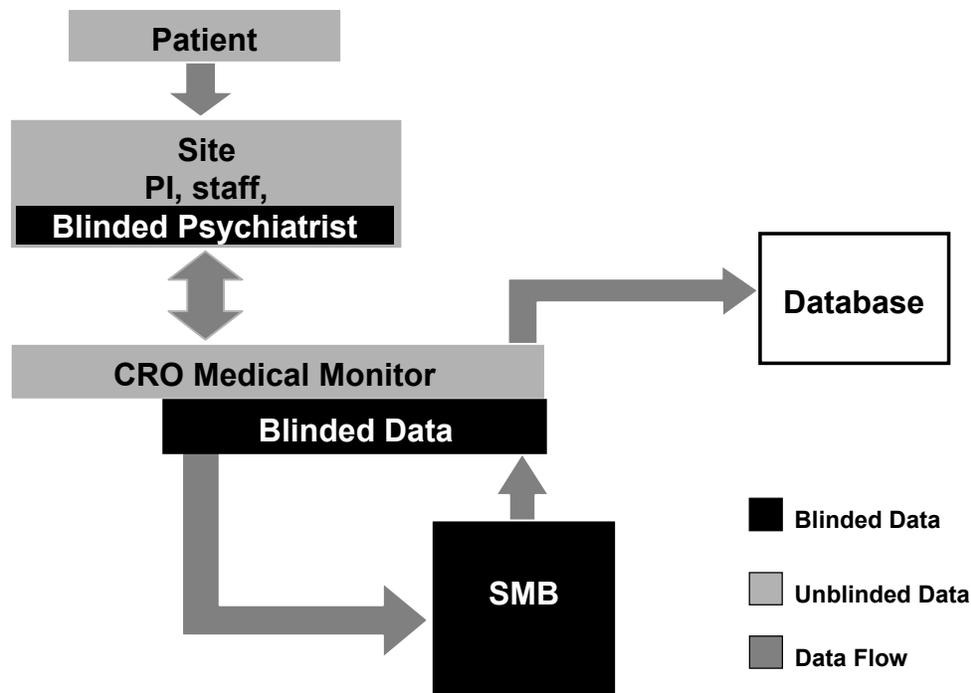
For case material being forwarded to the SMB and the BP, the Medical Monitor eliminated any mention in the study documents of the patients' study medication and any signs/symptoms that might have revealed their assigned treatment (e.g. hypersalivation, dystonias, WBCs, excessive drowsiness).

The database was maintained by the CRO, and transferred to the sponsor after all data were cleaned, coded and locked for the final analyses.

- **Suicide Monitoring Board**

The three members of the Suicide Monitoring Board (SMB) were selected on the basis of their expertise in the areas of suicidology and schizophrenia research. The SMB was independent of the investigative sites and study sponsor. Its role was to decide whether a potential primary endpoint met criteria for a suicide attempt or a hospitalization to prevent suicide (Type 1 event). In this role, the SMB received only blinded data from the Medical Monitor.

Figure 2 Data Flow in the Determination of Suicide Attempt/Hospitalization to Prevent Suicide



4.5 Statistical Methods

All efficacy analyses were based on data from the intent-to-treat (ITT) population, which was defined as all patients randomized to treatment. The safety population consisted of all patients that received study medication. For those patients who discontinued prematurely, every effort was made to follow them to their respective 2-year endpoint in order to determine whether a suicide attempt, suicide or a hospitalization to prevent suicide had occurred. These

patients were termed Retrieved Dropouts (RDOs) and were included in the ITT and safety populations.

4.5.1 Description of the Primary Analysis

As patients in this study may have experienced a Type 1 and a Type 2 event (e.g., a suicide attempt and a worsening on the CGI-SS-BP), the approach of Wei, Lin, and Weissfeld (1989), commonly known as the WLW method, was used for the primary analysis. The WLW method is a semi-parametric method used to analyze multivariate time-to-event data. This method models the marginal distribution with a Cox's proportional hazards model. No particular structure of dependence on each event time is imposed by this approach.

In accordance with the WLW approach, the time to the first occurrence of a Type 1 event and the time to the first occurrence of a Type 2 event were modeled, using the same proportional hazards model, with treatment group as the main effect and pooled country as stratum. Data from countries in which less than 50 patients were randomized were pooled based on geography and/or similar medical practice.

The WLW method provides consistent estimates of treatment effects and their robust standard errors for Type 1 and Type 2 events. These are then combined to develop a single overall test for the null hypothesis of no treatment effect at the 5% level of significance.

The combined estimator of treatment effect was defined as:

$$\hat{\beta}_c = c \hat{\beta}_1 + (1-c) \hat{\beta}_2,$$

where $\hat{\beta}_1$ and $\hat{\beta}_2$ are the maximum partial likelihood estimators of β_1 and β_2 , respectively, and $1 \geq c \geq 0$. Here, β_1 and β_2 represents the treatment effects on Type 1 and Type 2 events, respectively.

In agreement with FDA, the value for 'c' in the above formula was fixed at 0.5, providing equal weight to both of these events.

4.5.2 Supportive Analyses of Type 1 and Type 2 Events

Separate analyses of the time to Type 1 and time to Type 2 events were performed, each using the same Cox's proportional hazards regression model with the following explanatory variables: treatment, number of lifetime suicide attempts, active substance/alcohol abuse, pooled country, gender and age group (18-32, 33-44, and ≥ 45 years).

In addition, Kaplan-Meier estimates of cumulative probability of experiencing a Type 1 or Type 2 event were computed.

4.5.3 Secondary Analyses

The planned analyses for the secondary efficacy endpoints were as follows:

- 1) Change from baseline in total score on the ISST-BP.
- 2) Change from baseline in the 7-point CGI-SS-BP change scale score.

For both of these efficacy variables, descriptive statistics were reported for each visit where assessments were made and at the end of the study, as applicable. The two treatment groups were compared using an analysis of covariance (ANCOVA) model, with change from baseline to the end of study as the dependent variable and the following explanatory variables:

Treatment, pooled country, gender and the following measurements at baseline: age group, number of lifetime suicide attempts, CGI-SS-BP, ISST-BP, CDS total score, diagnosis, substance or alcohol abuse, ESRS total score, total Lindenmayer's PANSS positive syndrome subscale, hopelessness score and Covi Anxiety Scale total score.

- 3) Change from baseline in PANSS total score and subscale scores.
- 4) Change from baseline in the total score of the CDS.
- 5) Change from baseline in the total score of the Covi.

For the PANSS, CDS and Covi, the main analysis used ANCOVA model with treatment, pooled country and baseline total scores as explanatory variables to compare change from baseline between the two treatment groups. Wilcoxon Signed-Rank test provided p-values to test whether change from baseline score was different from 0 within treatment.

4.6 Results

4.6.1 Patient Disposition and Demographics

There were 67 centers in 11 countries (United States, Canada, Chile, Argentina, United Kingdom, France, Italy, Hungary, Czech Republic, Croatia, and South Africa). The United States, United Kingdom, France and Hungary randomized 78% of the patients (40.4%, 11.3%, 10.2% and 10.1%, respectively). A total of 1065 patients were screened, of whom 980 were randomized in 1:1 ratio to treatment with Clozaril or Zyprexa. The ITT population comprised 980 randomized patients (490 patients per treatment group); 479 patients in the Clozaril group and 477 in the Zyprexa group actually received study medication. Approximately 60% of the patients completed the study. (Table 4.1)

Of the 192 and 188 patients in the Clozaril and Zyprexa groups, respectively, who discontinued study treatment, 73 (38%) Clozaril and 88 (47%) Zyprexa patients experienced a Type 1 or Type 2 event either before discontinuation, or were followed up to the end of the 2-year observation period (RDOs). Therefore, only 119 (24%) Clozaril and 100 (20%) Zyprexa patients were considered as dropouts in the primary efficacy analysis

Table 4.1 Patient Disposition

	Patients, n (%)	
	Clozaril	Zyprexa
Screened	1,065 total	
Randomized (ITT population)	490 (100)	490 (100)
Treated	479 (97.8)	477 (97.3)
Completed	298 (60.8)	302 (61.6)
Discontinued	192 (39.2)	188 (38.4)

With few notable differences, the number of patients who discontinued the study and reasons for discontinuation were similar for both treatment groups. No Zyprexa patient dropped out because of abnormal lab values and procedures, and no Clozaril patient discontinued due to unsatisfactory effect on suicide risk (Table 4.1.2).

Table 4.1.1 Reasons for Discontinuation

	Patients, n (%)	
	Clozaril N = 490	Zyprexa N = 490
Withdrawn consent	50 (10.2)	49 (10.0)
Adverse event	41 (8.4)	33 (6.7)
Lost to follow-up	33 (6.7)	39 (8.0)
Protocol violation	29 (5.9)	20 (4.1)
Administrative reasons	23 (4.7)	27 (5.5)
Unsatisfactory effect on psychosis	5 (1.0)	9 (1.8)
Death	8 (1.6)	5 (1.0)
Unsatisfactory effect on suicide risk	0 (0.0)	6 (1.2)
Abnormal lab value	2 (0.4)	0 (0.0)
Abnormal procedure result	1 (0.2)	0 (0.0)
Total (380, 39%)	192 (39.2)	188 (38.4)

There were no significant differences in the demographic characteristics of patients treated with Clozaril or Zyprexa. For both treatment groups, the mean age was 37 years, 60% of patients were male, 70% were white, 15% were black, 1% oriental and 12% other races (Table 4.2).

Table 4.2 Demographics at Baseline

		Patients, n (%)	
		Clozaril N = 490	Zyprexa N = 490
Age, years	18 - 32	168 (34.3)	178 (36.3)
	33 - 44	216 (44.1)	204 (41.6)
	≥ 45	106 (21.6)	108 (22.0)
Males		301 (61.4)	301 (61.4)
Race	Caucasian	356 (72.7)	337 (68.8)
	Black	65 (13.3)	86 (17.6)
	Oriental	6 (1.2)	7 (1.4)
	Other	63 (12.9)	60 (12.2)

Approximately two thirds of the patients in both treatment groups had a baseline diagnosis of schizophrenia, approximately one third had a diagnosis of schizoaffective disorder, and about one fourth of the patients in each treatment group were treatment resistant by history (Table 4.3).

Table 4.3 Diagnosis at Baseline

	Patients, n (%)	
	Clozaril N = 490	Zyprexa N = 490
Schizophrenia	300 (61.2)	309 (63.1)
Schizoaffective disorder	190 (38.8)	181 (36.9)
Treatment resistant	135 (27.6)	128 (26.1)

The baseline clinical characteristics of patients in both treatment groups were very similar. Underscoring the fact that this was a high risk population, nearly 85 % of the patients had made at least one previous suicide attempt during their lifetime, 85% had been hospitalized to prevent a suicide attempt and 63% had made at least one suicide attempt in the past 36 months. For both treatment groups the age at onset of illness was about 25 years. Acute baseline psychopathology and an appreciable level of depressive symptomatology were also apparent and similar in both the Clozaril and Zyprexa treatment groups. These characteristics are summarized in Table 4.4 below:

Table 4.4 Clinical Characteristics at Baseline

	Mean ± SD	
	Clozaril	Zyprexa
Age at onset, years	24.9 ± 8.6	24.4 ± 8.3
CGI-SS-BP [§]	2.2 ± 1.0	2.2 ± 1.0
ISST-BP	7.4 ± 5.7	7.3 ± 5.7
Lifetime suicide attempts	3.6 ± 7.5	3.2 ± 4.5
Lifetime hospitalizations to prevent suicide	3.7 ± 7.7	3.2 ± 4.8
PANSS-T	84.8 ± 21.1	82.6 ± 20.9
CDS	9.8 ± 5.9	9.9 ± 5.9
Covi Anxiety Scale	3.8 ± 2.7	3.9 ± 2.7

•§2 = Mildly suicidal; 3 = Moderately suicidal.

4.6.2 Study Medication

The mean daily dose during the 2-year study was 274 mg for Clozaril and 17 mg for Zyprexa. No patient in the Clozaril group received more than the recommended maximum Clozaril dose of 900 mg/day, whereas 111 patients (23%) in the Zyprexa group received approximately twice the recommended maximum dose of 20 mg/day (Table 4.5).

Table 4.5 Study Medication

	Clozaril N = 479	Zyprexa N = 477
Total daily dose, mg		
Mean ± SD	274 ± 155	17 ± 6
Median	262	17
Range	12.5 - 725	2.5 - 41.0

Analysis of mean exposure to study medication by dosage category shows that, in the Clozaril group, 47.6% of the patients were prescribed dosages equal to or less than 250 mg/day and no patient was prescribed the maximum recommended dosage of 900 mg/d. In the Zyprexa group, 4.8% of patients were prescribed dosages lower than 8 mg/day, 76.7% were prescribed a dosage of >8 to 20 mg/day, and 18.4% were prescribed a dosage above the recommended maximum (>20 to <41 mg/day). For both treatment groups, the mean number of days on treatment increased with increasing dosage (Table 4.6).

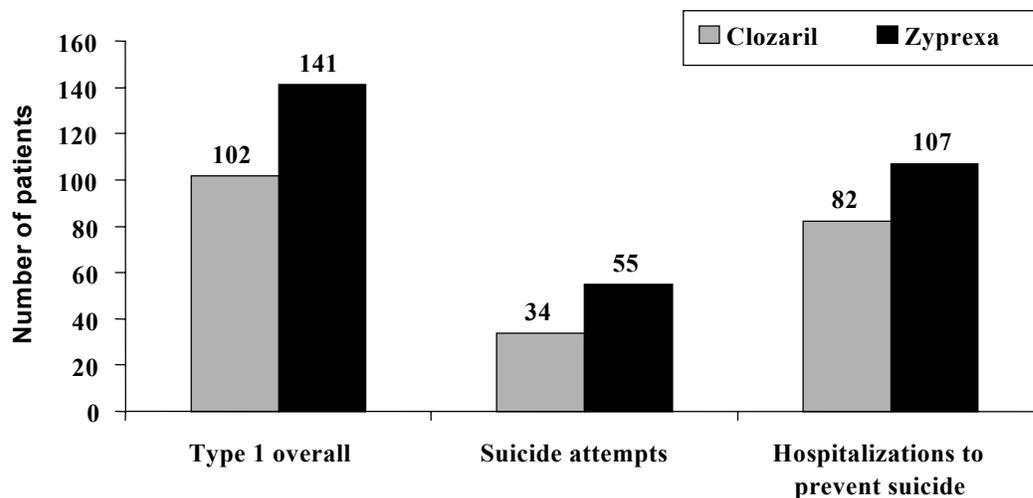
Table 4.6 Exposure to Study Medication by Dosage Category

Prescribed Dose Groupings	Patients n (%)	Mean Days on Treatment (SD)	Range of Days On Treatment
Clozaril			
≥ 0 and ≤ 250	227 (47.6)	400.9 (319.11)	6, 802
> 250 and ≤ 450	183 (38.4)	609.9 (227.27)	14, 851
> 450 and ≤ 725	67 (14.0)	670.1 (152.79)	64, 736
Zyprexa			
≥ 0 and ≤ 8	23 (4.8)	455 (334.59)	1, 735
> 8 and ≤ 20	366 (76.7)	545.5 (264.91)	1, 900
> 20 and ≤ 41	88 (18.4)	622.9 (199.45)	38, 765

4.6.3 Primary Efficacy Results

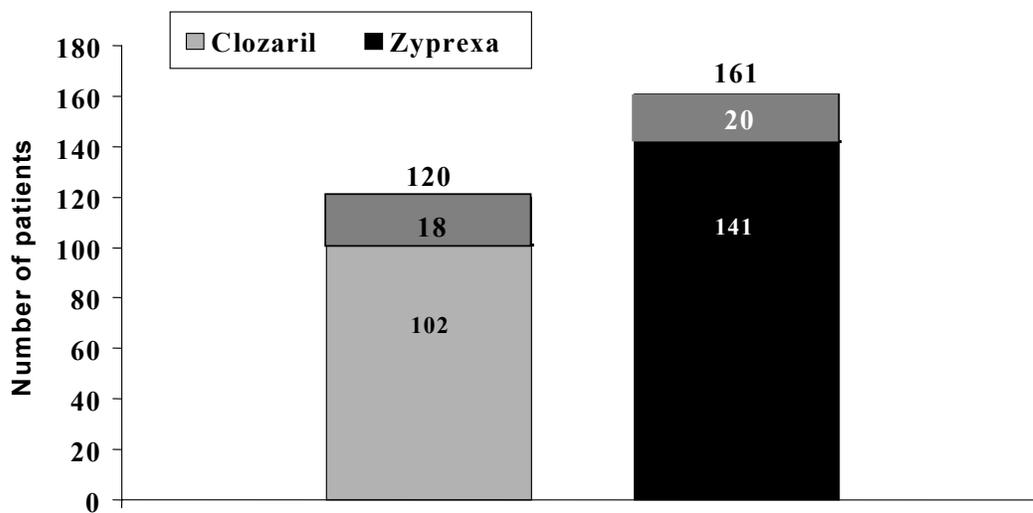
The Suicide Monitoring Board reviewed 577 potential Type 1 events. Of these, 483 events from 243 patients were determined by the SMB to be either suicide attempts, suicides or hospitalizations to prevent suicide. As shown in Figure 3, in the Clozaril treatment group 102 patients made a suicide attempt or were hospitalized to prevent suicide (i.e. Type 1 event), whereas 141 patients in the Zyprexa group experienced Type 1 events during the study. Thirty-four Clozaril-treated patients attempted suicide and 82 were hospitalized to prevent suicide, compared to 55 and 107 patients, respectively, in the Zyprexa group (Figure 3).

**Figure 3 Patients Experiencing SMB-Determined Type 1 Events
Suicide Attempts and Hospitalizations to Prevent Suicides**



Type 2 events represent either a worsening on the CGI-SS-BP or a Type 1 event that indicated an implicit worsening of suicidal behavior. There were fewer Type 2 events in the Clozaril group (120) than in the Zyprexa group (161)(Figure 4). However, only 18 patients in the Clozaril group and 20 patients in the Zyprexa group actually experienced a worsening of suicidal behavior as determined by the change in the CGI-SS-BP score, indicating that the difference between the treatment groups with regard to Type 2 events derived for the most part from the inclusion of Type 1 events in the definition of this endpoint.

Figure 4 Patients Experiencing Type 2 Events: Worsening of Severity of Suicidality, Suicide Attempt, Hospitalization to Prevent Suicide



4.6.3.1 Results of the Primary Efficacy Analysis and Supportive Analyses:

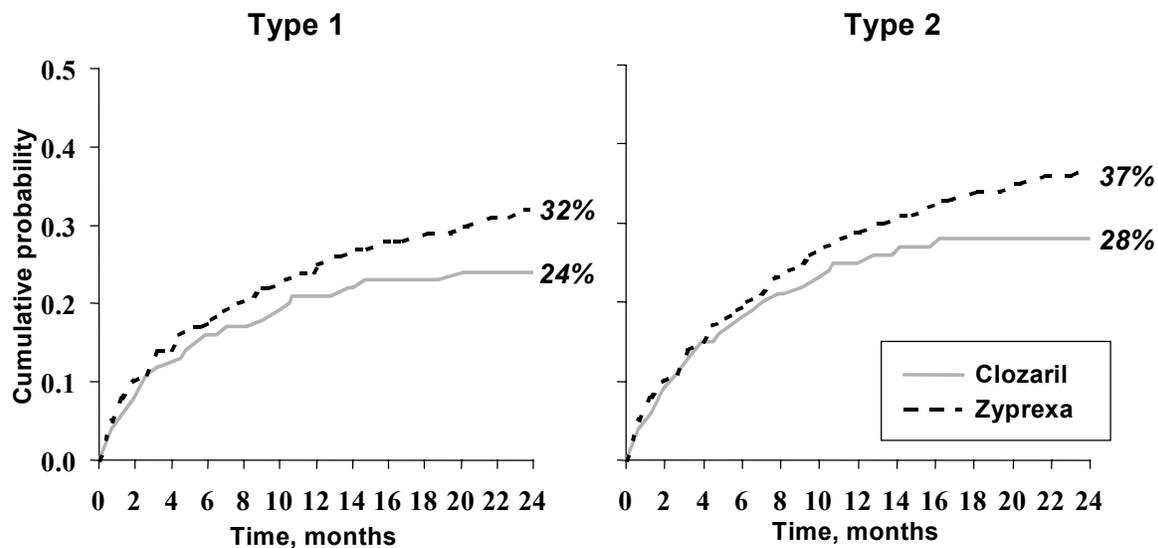
The primary efficacy analysis using the WLW method showed a statistically significant difference between the treatment groups in favor of Clozaril ($p = 0.031$, Table 4.6). Analysis using the Cox's proportional hazard regression model described in Section 4.5.2 demonstrates a 26% reduced risk for suicide attempt or hospitalization to prevent suicide (Type 1 event) for patients randomized Clozaril treatment compared to Zyprexa treatment ($p=0.02$, hazard ratio 0.74 [95% C.I.: 0.57,0.96]). Confirmatory analysis using a Cox's model including treatment-by-pooled-country interaction showed consistency of efficacy results across countries ($p=0.422$). Similarly, the treatment difference for Type 2 events was statistically significant in favor of Clozaril, with a hazard ratio of 0.76 (95% C.I.: 0.60,0.97), i.e., a 24% lower risk of experiencing a Type 2 event (Table 4.6).

Table 4.7 Results of WLW and Cox’s Proportional Hazard Analyses

	Hazard ratio	95% CI	P value
WLW analysis			.031
Cox’s proportional hazard analysis			
Type 1	0.74	0.57, 0.96	.021
Type 2	0.76	0.60, 0.97	.026

Kaplan-Meier estimates of cumulative probabilities for Type 1 and Type 2 events were calculated for the two treatment groups and are depicted in Figure 4.5. The cumulative probability of experiencing a Type 1 or a Type 2 event was consistently lower for Clozaril patients than for Zyprexa patients during the study, and the difference between the two treatment groups increased appreciably after 6 months. For the last 12 months of the study the cumulative probability of experiencing an event remained fairly constant for the Clozaril-treated patients, whereas it continued to increase for the Zyprexa-treated patients. At week 104 (end of study), the cumulative probability of having a Type 1 event was 24% for the Clozaril group compared to 32% for the Zyprexa group (95% C.I. of the difference: 2%, 14%). As could be expected from the preponderance of Type 1 events in the Type 2 data set, there was a lower probability of experiencing a Type 2 event in the Clozaril group (Clozaril 28% compared to Zyprexa patients 37%; 95% C.I. of the difference: 2%, 15%).

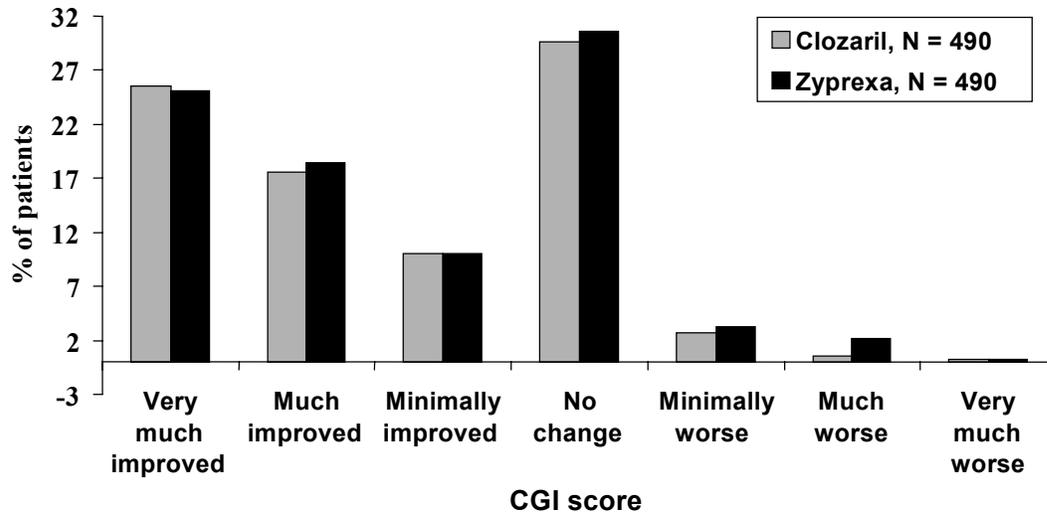
Figure 5 Kaplan-Meier Estimates of Cumulative Probability of a Type 1 or Type 2 Event



4.6.3.2 Secondary Efficacy Analyses

At week 104, similar proportions of patients in the treatment groups showed improvement, worsening, or no change in their severity of suicidal behavior relative to baseline as measured by the CGI-SS-BP (Figure 6).

**Figure 6 Change in Severity of Suicidality
 CGI-SS-BP-Week 104**



Analyses of the changes from baseline in the ISST-BP, PANSS total score, Calgary Depression Scale and Covi Anxiety Scale show significant and similar improvement from baseline for both the Clozaril and Zyprexa groups (Figures 7 and 8). For each clinical measure, the change from baseline was statistically significant in each treatment group ($p < 0.001$). The results of the ANCOVA for the changes from baseline in the secondary outcome measures between treatment groups show no significant differences (Figures 7-8).

Figure 7 LS Mean Change From Baseline ISST-BP, Week 104

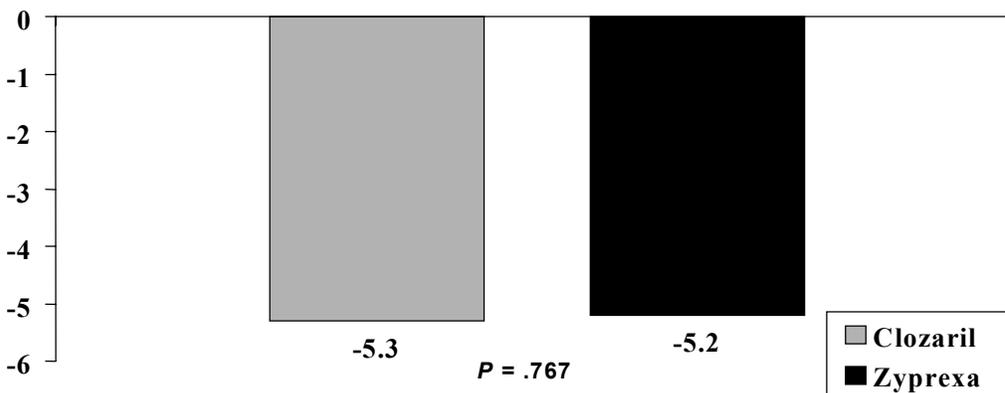
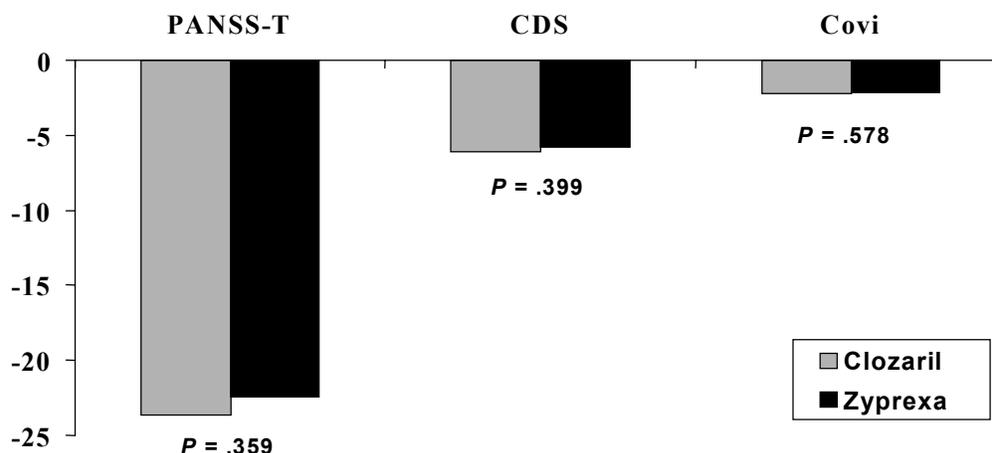


Figure 8 LS Mean Change From Baseline-Week 104 PANSS-T, CDS and Covi



4.6.3.3 Analysis of Concomitant Psychotropic Medication

The protocol allowed the use of adjunct antipsychotics, antidepressants, sedatives, anxiolytics and mood stabilizers. In order to evaluate the use of concomitant psychotropic medication in the two treatment groups, an analysis of the patients' exposure to all such agents during the trial was performed. The mean daily dose of psychotropic medication was calculated for the four classes of medication, using haloperidol equivalents for antipsychotics, diazepam equivalents for sedatives/anxiolytics, fluoxetine equivalents for antidepressants and carbamazepine equivalents for mood stabilizers. The results of this analysis show that for each of the four psychotropic classes, Clozaril patients received statistically significantly less concomitant medication than did Zyprexa patients (Table 4.8).

Table 4.8 LS Mean Daily Dose (mg) of Concomitant Psychotropic Medications

	Least square mean (\pm SE)		
	Clozaril	Zyprexa	P value
Antipsychotics ¹	2.1 \pm 0.3	3.8 \pm 0.3	< .001
Antidepressants ²	16.7 \pm 1.1	20.7 \pm 1.0	.001
Sedatives/ Anxiolytics ³	6.3 \pm 0.6	10.1 \pm 0.6	< .001
Mood Stabilizers ⁴	487.3 \pm 43.2	620.6 \pm 39.9	.011

¹Haloperidol, ²fluoxetine, ³diazepam, ⁴carbamazepine equivalents.

5 Safety Analyses

5.1 Adverse Events and Serious Adverse Events

Both Clozaril and Zyprexa are marketed medications for the treatment of schizophrenia, and extensive safety data has been collected for both agents. Adverse events occurring in this study were generally consistent in nature and frequency with clinical experience and current product labeling.

The overall incidence of AEs and SAEs was similar for both Clozaril and Zyprexa, with more than 90% of patients in each treatment group experiencing an adverse event during the 2-year study and approximately 50% in each treatment group experiencing a serious adverse event (Table 5.1).

Table 5.1 Incidence of Adverse Events and Serious Adverse Events

	Patients, n (%)		P value
	Clozaril N = 479	Zyprexa N = 477	
AEs	443 (92.5)	450 (94.3)	.297
SAEs	231(48.2)	235 (49.3)	.796

Table 5.2 shows that, consistent with current prescribing information, Clozaril-treated patients, when compared with those on Zyprexa, experienced a higher incidence of white blood cell decrease (5.8% vs 0.8%), , postural hypotension (4.4% vs 0.2%), salivary hypersecretion (47.8% vs 5.9%), constipation (25.1% vs 9.6%), weakness (7.5% vs 2.3%), and convulsions (2.5% vs 0.4%).

Relative to the Clozaril group, Zyprexa-treated patients experienced a higher incidence of dry mouth (9% vs 5.4%), weight increase (55.6% vs 31.1%), asthma (4.0% vs 1%), lacerations (4.0% vs 0.4%), and epistaxis (1.0% vs 0%). There were no cases of agranulocytosis, myocarditis, or cardiomyopathy in the Clozaril group, and there was one case of cardiomyopathy in the Zyprexa group. Diabetes mellitus was reported as an adverse event for 16 (3.1%) of the Clozaril-treated patients and 21 (4.4%) of the Zyprexa-treated patients (Table 5.3).

Table 5.2 Clozaril Adverse Events of Interest

Adverse reaction	Patients, n (%)		P value *
	Clozaril N = 479	Zyprexa N = 477	
White blood cell decrease	28 (5.8)	4 (0.8)	< .0001
Postural hypotension	21 (4.4)	1 (0.2)	< .0001
Salivary hypersecretion	229 (47.8)	28 (5.9)	< .0001
Constipation	120 (25.1)	46 (9.6)	< .0001
Weakness	36 (7.5)	11 (2.3)	< .001
Convulsions	12 (2.5)	2 (0.4)	.012

*Fisher's exact test.

Table 5.3 Zyprexa Adverse Events of Interest

Adverse reaction	Patients, n (%)		P value*
	Clozaril N = 479	Zyprexa N = 477	
Dry mouth	26 (5.4)	43 (9.0)	.034
Diabetes mellitus NOS	16 (3.3)	21 (4.4)	NS
Weight increased	150 (31.1)	265 (55.6)	< .0001
Asthma	5 (1.0)	19 (4.0)	.004
Laceration	2 (0.4)	19 (4.0)	<.001
Epistaxis	0	5 (1.0)	.031

*Fisher's exact test.

Statistically significant differences between groups.

Of the neuropsychiatric adverse events that were reported, Zyprexa treatment was associated with a higher occurrence of depression, suicidal ideation, suicide attempt, drug abuse, tension, mood disorder, insomnia, and akathisia than Clozaril treatment. Treatment with Clozaril was associated with a higher occurrence of sedation, dysarthria and syncope (Table 5.4).

Table 5.4 Neuropsychiatric Adverse Events

Adverse reaction	Patients, n (%)		P value*
	Clozaril N = 479	Zyprexa N = 477	
Depression	137 (28.6)	173 (36.3)	.013
Suicidal ideation	125 (26.1)	153 (32.1)	.046
Suicide attempt	37 (7.7)	66 (13.8)	.002
Drug abuse	4 (0.8)	14 (2.9)	.018
Tension	3 (0.6)	11 (2.3)	.034
Mood disorder	0	8 (1.7)	.004
Insomnia	96 (20.0)	155 (32.5)	< .0001
Akathisia	21 (4.4)	39 (8.2)	.016
Sedation	220 (45.9)	118 (24.7)	< .0001
Dizziness	129 (26.9)	59 (12.4)	< .0001
Dysarthria	23 (4.8)	2 (0.4)	< .0001
Syncope	15 (3.1)	5 (1.0)	.039

*Fisher's exact test.

5.2 Deaths

There were 22 deaths during InterSePT. Twenty of these deaths occurred during the 2-year treatment period (12 Clozaril patients and 8 Zyprexa patients p=0.499), while two occurred after completion of the study but within the 30-day safety follow-up period. Causes of death for Clozaril and Zyprexa-treated patients are listed in Table 5.5. Narratives on each death can be found in Appendix 2. Other than suicide and cancer, the causes of death are mostly cardiovascular in nature for both treatment groups.

Table 5.5 Total Deaths

Cause of death	Patients, n	
	Clozaril	Zyprexa
Suicide	5 (1)*	3 (1)*
Cardiac arrhythmia	2	1
Coronary artery disease	1	
Myocardial infarction		1
Cardio-respiratory arrest		2
Stroke	1	
Pulmonary embolism	1	
Car accident	1	
Lymphoma	1	
Carcinoma		1
Total	12 (1)*	8 (1)*

* death occurred after the study but within safety follow-up period.

6 DISCUSSION

Suicidal behavior carries an enormous emotional and economic burden for schizophrenic and schizoaffective patients and their families. It is a clinical problem that leads to a large number of hospital admissions and in many cases to long-term physical disability. InterSePT is the first prospective, well-controlled study specifically designed to address this major public health problem. This study included patients with schizophrenia or schizoaffective disorder who were at risk for suicide. Reduction in the risk of suicidal behavior, as measured by suicide attempts and hospitalizations for imminent risk of suicide, was the objective upon which the efficacy analyses were based. The study design maximized patient safety and allowed every effort to be made to prevent suicide. The study protocol, in particular the definitions of endpoints for suicidal behavior and the statistical analysis, was developed in collaboration with the FDA.

The results of the efficacy analysis indicate a statistically significant reduction in the risk for suicidal behavior with Clozaril treatment compared to Zyprexa treatment ($p=0.031$). Specifically, it was shown that Clozaril reduces the risk of a suicide attempt or hospitalization to prevent suicide by 26% compared to Zyprexa ($p=0.021$).

The clinical significance of this superiority for Clozaril in reducing the risk for suicidal behavior is enhanced by the fact that Clozaril-treated patients received significantly less concomitant psychotropic medication than those in the Zyprexa group.

Analyses of the clinical measures CGI-SS-BP, ISST, PANSS-T Score, Calgary Depression Scale and Covi Anxiety Scale show significant and similar improvement from baseline for both Clozaril and Zyprexa. The obvious absence of any relationship between these results and the results of the WLW and Cox's proportional hazard analyses indicates that the Clozaril effect on reducing suicide attempts and hospitalizations for imminent risk of suicide is independent of observed changes in clinical status. These results support the hypothesis that suicidal behavior is a separate domain from psychosis in schizophrenia and schizoaffective disorder.

The pattern of adverse events observed for Clozaril and Zyprexa in this study is consistent with previous clinical experience. Given the high-risk background of the patient population, it was perhaps inevitable that some suicide attempts were successful despite extensive efforts at the sites to prevent such events. Although there were 2 more suicides in the Clozaril treatment group than the Zyprexa group, the difference is not statistically significant ($p=0.522$). In any case, the total of 10 suicides in 980 high-risk patients over two years can be considered low.

Based on the results of this two-year study, it has been calculated that 13 patients would need to be treated (NNT)¹ with Clozaril to prevent one suicide attempt/suicide/hospitalization relative to Zyprexa.

Overall, the results of InterSePT indicate that the benefits of Clozaril in the treatment of suicidal behavior outweigh the safety risks associated with its use.

¹ The number needed to treat (NNT) = $1/(\text{control event rate} - \text{experimental event rate}) = 1/(0.32-0.24)=12.5 \sim 13$

7 CONCLUSIONS

- Over a period of 2 years, treatment with Clozaril compared with Zyprexa was associated with a 26% reduction of risk for suicide attempts and hospitalizations to prevent suicide.
- This reduction of risk appears not to be attributable to a greater effect on psychotic or depressive symptoms or to greater use of concomitant psychotropic medications.
- Adverse event profiles for both study drugs were generally consistent with previous experience and current product labeling.
- The benefits of treatment with Clozaril in this patient population outweigh the safety risks associated with its use.

The results of InterSePT show that Clozaril is effective in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder and support the following indication:

CLOZARIL is indicated for reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for emergent suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at high risk for death.